CIRCULATORY CHANGES AT BIRTH

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Introduction

Before birth, oxygenation of the fetus occurs at the placental site. Oxygenated blood is carried to the fetus through the umbilical veins; about 50% of umbilical venous blood passes through the hepatic microcirculation, but the remainder traverses the ductus venosus to the inferior vena cava (1). In the thoracic portion of the inferior vena cava, there is streaming of the well-oxygenated ductus venosus blood so that it is preferentially directed through the foramen ovale into the left atrium and left ventricle. The poorly oxygenated blood from the abdominal inferior vena cava is preferentially distributed through the tricuspid valve into the right ventricle (2, 3). This streaming pattern in the inferior vena cava, combined with the fact that almost all of the poorly oxygenated blood returning to the heart through the superior vena cava passes through the tricuspid valve, explains the presence of a higher oxygen saturation in left ventricular blood, as compared with right ventricular, in the fetus. Most of the blood ejected by the right ventricle into the pulmonary trunk bypasses the pulmonary circulation by being distributed through the ductus arteriosus directly into the descending aorta. Only a small proportion of blood ejected by the left ventricle traverses the aortic isthmus to the descending aorta, most being distributed to the head, neck, and forelimbs (4).

The foramen ovale and ductus arteriosus serve the important role of diverting blood returning to the heart away from the lungs. During fetal life, the lungs do not serve the function of gas exchange; therefore, only a small blood flow is required for metabolic func-

tions. Were the foramen ovale not present, the total volume of fetal venous blood, including all umbilical venous as well as superior and inferior vena caval return, would have to be ejected by the right ventricle, thereby imposing a considerable unnecessary load on that ventricle. Similarly, in the absence of a ductus arteriosus, all blood ejected by the right ventricle would have to pass through the lung and return to the left ventricle, thus placing a considerable extra burden on this ventricle.

Although there is considerable streaming of umbilical venous and fetal body venous blood, the bloods do mix centrally, so that blood distributed to the fetal body as well as back to the placenta contains a mixture derived from all sources of venous return. Only a very small proportion of superior vena caval blood is, however, distributed back to the upper body.

After birth, the adult type of circulation is established, consisting of series flow of venous blood to the right atrium and ventricle, which ejects total cardiac output into the lungs, whence it returns to the left atrium and ventricle to be ejected into the aorta. There is thus no significant mixing of oxygenated arterial and poorly oxygenated venous blood. The term *cardiac output* as applied to the postnatal circulation represents the volume of blood ejected by each ventricle per minute because it refers to the volume of blood circulating in the series circuit. This concept cannot be applied in the fetus because the oxygenated and systemic venous bloods mix and are distributed both to the fetal body and to the lungs. The term *combined ventricular output* has therefore been used to designate the total volume of blood ejected by the two ventricles per minute.

To establish the adult type of circulation, several important events have to occur after birth. The umbilical-placental circulation is removed by separation of the umbilical cord, and adequate pulmonary circulation must be developed to provide oxygen to the body; also, the foramen ovale and ductus arteriosus must close. The factors responsible for effecting these changes have been examined to some extent, but separating the role of specific events that occur around birth has been difficult. Several studies were

conducted in lambs exteriorized from the uterus, but with intact umbilical placental circulation (5). In similar preparations, the effects of ventilation were studied in anesthetized, open-chest lambs (6). Another approach to assessing changes after birth has been to compare measurements made in unanesthetized lambs some days after birth with those made in unanesthetized fetal lambs *in utero*. These studies have led to the current concepts that pulmonary blood flow increases markedly after birth, and that, although physical expansion of the lung alone with no change in blood gases has a small effect, the major factor responsible for the postnatal decreases in pulmonary vascular resistance is the increase in alveolar and pulmonary venous PO_2 (6). It has also been thought that elimination of the umbilical-placental circulation results in a marked increase in systemic vascular resistance, and that this is responsible for reversal of blood flow through the ductus arteriosus from the aorta to the pulmonary circulation. Furthermore, it has been thought that the main factor responsible for closure of the ductus arteriosus was the increase in aortic PO_2 (7, 8).

Measurements in newborn lambs have shown that heart rate is higher than in the fetus and that resting cardiac output (measured as the output of both ventricles to compare with the combined ventricular output of the fetus) is considerably higher (9, 10). These measurements were made two to three days after birth, so the exact time after birth that the changes occurred was not known.

Animal Model

To attempt to define the effects of some of the specific events that occur at the time of birth, we have developed a model for studying fetal lambs *in utero*. By studying the lamb within the uterus, we could avoid the interference of surface cooling and of handling, which could contribute to circulatory changes. We were able to study the effects of rhythmic ventilation alone without changing fetal blood gases, and then to examine the changes associated with oxygenation. Finally, we studied the response to occluding the umbilical cord *in utero* while the fetus was well oxygenated and ventilated. Another advantage of this preparation is that it

is possible to assess the importance of some of the hormonal changes that occur immediately prior to delivery. It is well known that fetal plasma cortisol and thyroid hormone concentrations increase in the two to three days prior to birth of the lamb (11). The role of these hormonal changes on the circulatory adaptations after birth has not been well defined, although prenatal thyroid hormone is known to be important for the rise in heart rate and cardiac output after birth (12). By studying lambs before the hormonal changes have occurred and after administering selective hormones to simulate the rise that normally occurs prenatally, it will be possible to assess their importance.

We prepared 133-135 day gestation fetal lambs for study (term is ~145 days). The ewe was given epidural anesthesia and intravenous ketamine sedation. Through an abdominal incision, the uterus was exposed, and through uterine incisions over the hindlimb and over the upper left thorax, the fetus was approached. Using local anesthesia, catheters were placed in a hindlimb artery and vein. Through the fourth left intercostal space, catheters were inserted into the pulmonary trunk and left atrium and the chest closed by suturing muscle layers and skin. The head and neck were then exposed, and catheters were inserted into an external jugular vein and carotid artery. A 4.5 mm tracheal tube was passed so that its tip was in the trachea just within the thorax; it was attached to two #12 F tubes by means of a Y-connector. Through the same uterine incision, the umbilical cord was identified at the site of attachment to the abdomen, and an inflatable silicone balloon occluder was placed around it; the balloon could be inflated by injecting fluid into it through an attached catheter, resulting in umbilical vessel obstruction, which could be complete. After replacing the fetal head, the uterine incision was sutured. All catheters, including the two tracheal tubes, were led through the left maternal flank to be stored in a cloth pocket sewn to the maternal skin. The ewe and lamb were allowed to recover for two to three days; the lambs were then studied while the ewe stood quietly in a stall with access to food and water.

Fetal arterial, pulmonary arterial, left atrial, and venous pressures were measured continuously, and the heart rate, triggered

from the arterial pressure pulse, was recorded beat-to-beat by means of a cardiotachometer. Blood gases and oxygen saturations were measured in each vessel during a control period and after each manipulation. Similarly, at each period combined ventricular output and its distribution as well as organ blood flows were measured by the radionuclide-labeled microsphere technique. We injected microspheres labeled with different gamma labels simultaneously into the hindlimb and left atrial catheters while blood was being withdrawn, for reference samples, from the pulmonary trunk and carotid and femoral arterial catheters. With these simultaneous injections and withdrawals, we could calculate the combined ventricular output, individual outputs of the left and right ventricles, shunts through the foramen ovale and ductus arteriosus, pulmonary blood flow, and flow to all other fetal organs and the placenta. These calculations have been described in detail (13, 14).

After making measurements during the control period, similar measurements were made during three subsequent periods:

1) The tracheal tubes were cleared of fluid and the lamb was ventilated by rhythmic expansion of the lungs with a gas consisting of about 3% oxygen and 6-7% CO_2 with the balance nitrogen. This gas mixture was chosen because the PO_2 was about 21 torr, and the PCO_2 42-49 torr, tensions similar to those in fetal blood. Using this mixture, fetal blood gases did not change significantly, so it was possible to examine the effects of rhythmic physical expansion of the lungs alone. Pressures, blood gases, and microsphere studies were measured about 15 min after the onset of ventilation.

2) Ventilation was continued, but the gas was changed to pure oxygen, with about 3-6% CO_2, sufficient to maintain fetal arterial PCO_2 constant. Again measurements were repeated about 15 min after oxygen was instituted

3) While continuing to ventilate with oxygen, the occluder on the umbilical cord was inflated to produce complete occlusion. After 15 min of occlusion, studies were repeated.

Ventilation was performed with a specially-designed respiratory pump. A continuous rapid flow of gas was maintained through the tubes during the expiratory phase to wash expired gas out of the long lengths of tubing, and thus dead space was reduced. During the inspiratory phase, positive pressures of about 25 mm Hg above amniotic cavity pressure were used. Ventilatory rates during the three phases were similar at 50 ± 9, 54 ± 10, and 56 ± 12 per min, respectively. The peak positive pressures reached during inspiration were 27 ± 10, 25 ± 10, and 25 ± 8 mm Hg above amniotic pressure during each of the three periods. Also, we found it was necessary to maintain an end-tidal pressure of 3-15 mm Hg above amniotic pressure to achieve effective lung expansion. We adjusted the inspiratory and end-expiratory pressures to achieve tidal volumes, as measured with a pneumotachograph, of 25-40 ml. The actual tidal volumes achieved during the three periods were 24 ± 15, 37 ± 16, and 31 ± 1 ml, respectively.

Effects of Rhythmic Lung Expansion

Rhythmic expansion of the lungs with the gas containing 3% oxygen produced no significant changes in fetal blood gases. Heart rate, which during the control period was 173 ± 25 per min, fell dramatically to below 100 per min with initiation of lung expansion, but within a few seconds, once rhythmic ventilation was established, it returned to a level of 152 ± 16 per min, which was slightly but not statistically significantly below control. Pressures in the aorta and pulmonary artery did not change significantly, but left atrial pressure increased from 3 ± 3 to 6.9 ± 4 mm Hg.

The combined ventricular output did not change significantly from its control value of 398 ± 81 ml/min/kg fetal weight. There was a striking increase in pulmonary blood flow from 136 ± 75 to 778 ± 513 ml/min/100 g lung weight. Pulmonary vascular resistance, calculated from mean pressure difference across the lung (mean pulmonary arterial minus left atrial mean pressure) divided by pulmonary blood flow, decreased markedly from the control value 0.44 ± 0.24 mm Hg/ml/min/100 g to 0.16 ± 0.29. There was considerable variability in the response, with some lambs showing very little change

and others showing a marked fall in pulmonary vascular resistance with rhythmic lung expansion alone.

Although combined ventricular output did not change significantly, the proportions of blood ejected by each ventricle were altered. Normally in the lamb, the right ventricle ejects about two-thirds of the total output and the left, one-third (4, 13). In this series, during the control period right ventricular output was 258 ± 69 and left ventricular output 134 ± 44 ml/min/kg fetal weight, representing 66% and 34% of combined ventricular output, respectively. With lung expansion, right ventricular output fell slightly to 225 ± 69 ml/min/kg, but left ventricular output increased considerably to 211 ± 87 ml/min/kg, so that the right ventricle now contributed only 52%, whereas the left ventricle comprised 48% of combined ventricular output.

Associated with the increase in pulmonary blood flow, flows through the ductus arteriosus and foramen ovale also changed. During the control period, 57% of the combined ventricular output traversed the ductus arteriosus from the pulmonary trunk to the descending aorta and thus fell to 24% during rhythmic lung expansion; in addition, a small flow from the aorta to pulmonary artery of 3% of combined ventricular output could be calculated. Blood flow through the foramen ovale from the inferior vena cava and right atrium fell from 27% of combined ventricular output during control to 17% during lung expansion.

Blood flow to the carcass (skin, muscle, and bone) fell significantly from 15.3 ± 3.2 to 11.1 ± 4.0 ml/min/100 g tissue weight. Also, gastrointestinal blood flow fell significantly. There were also small, but not significant, changes in blood flow to the kidneys and brain, and in umbilical-placental blood flow.

Ventilation with Oxygen

Ventilation of the fetus with oxygen resulted in a marked increase of fetal arterial PO_2 from 19 ± 4 to 171 ± 164 torr. Heart rate was not significantly different from control levels. Aortic mean

pressure fell from 53 ± 6 to 47 ± 6 mm Hg, and pulmonary arterial mean pressure fell from 55 ± 7 to 47 ± 6 mm Hg during oxygenation; mean left atrial pressure increased further to 8 ± 4 mm Hg.

Combined ventricular output did not change significantly from control values. Pulmonary blood flow increased even further, from 778 ± 513 ml/min/100 g lung weight during rhythmic lung expansion to 1139 ± 406 ml/min/100 g during ventilation with oxygen. Pulmonary vascular resistance fell further from the level of 0.44 ± 0.24 mm Hg/ml/min/100 g during ventilation alone to 0.04 ± 0.04 mm Hg/ml/min/100 g with oxygenation. As with rhythmic lung expansion, responses of individual lambs varied greatly. Thus, some animals showed very little pulmonary vasodilatation with lung expansion alone, but demonstrated a dramatic response with oxygenation. About half the lambs showed a major response to ventilation alone, and showed only a further small or no additional fall in pulmonary vascular resistance with oxygenation. A small number of animals demonstrated some change with ventilation and an additional similar response with oxygenation.

Associated with the increase in pulmonary blood flow, there was a further small increase in left ventricular output to 227 ± 64 ml/min/kg, whereas right ventricular output fell significantly from 225 ± 69 ml/min/kg during ventilation alone to 187 ± 47 ml/min/kg. Left ventricular output now exceeded right ventricular output with 55% of combined ventricular output being ejected by the left, and only 45% by the right, ventricle. Flow through the foramen ovale into the left atrium decreased markedly, with only 3-4% of combined ventricular output traversing the foramen. Flow through the ductus arteriosus from the pulmonary trunk to the aorta was almost completely abolished, with only about 4% of combined ventricular output flowing in this direction, but a flow of about 11% of combined ventricular output occurred from the aorta to the pulmonary arteries through the ductus arteriosus.

Blood flow to the carcass fell even further, from 11.1 ± 4 ml/min/100 g tissue during rhythmic expansion alone to 8.1 ± 3.1 ml/min/100 g during ventilation with oxygen. This represented almost 50% reduction of flow to the peripheral circulation from the control

values. Cerebral flow also fell dramatically from 135 ± 53 to 58 ± 21 ml/min/100 g, and blood flow to the myocardium also fell to less than 50% of control values in association with oxygenation. Thus, left ventricular myocardial flow fell from 238 ± 126 to 102 ± 37, and right ventricular myocardial flow fell from 280 ± 97 to 113 ± 30 ml/min/100 g. A further small but insignificant fall in flow to the umbilical-placental circulation occurred.

Effects of Umbilical Cord Occlusion

The umbilical cord was occluded while the fetus was being ventilated with oxygen. No significant changes in blood gases or pH occurred as compared with ventilation with oxygen. Heart rate fell slightly in some fetuses for several seconds, but rapidly recovered so that no statistically significant changes in heart rate were noted after 15 min. Aortic pressure increased immediately with cord occlusion, and this rise was sustained, with pressure leveling at about control values. However, pulmonary arterial pressure, which dropped with oxygenation;, fell even further so that there was a significant separation of aortic and pulmonary arterial pressure. Left atrial pressure increased even more, from 8 ± 4 mm Hg during oxygenation to 10 ± 4 mm Hg after cord occlusion.

Combined ventricular output did not change significantly, and there was no further change in pulmonary blood flow or in calculated pulmonary vascular resistance. Cord occlusion resulted in no further significant change in left ventricular output, but right ventricular output did fall slightly, though not significantly. This resulted in an even greater change in the ratios of left and right ventricular outputs, with 59% of combined ventricular output now being ejected by the left ventricle. Cord occlusion resulted in no further change in right-to-left flow through the foramen ovale to the left atrium, but left-to-right shunt through the ductus arteriosus increased further slightly. Occlusion of the cord caused a significant increase in gastrointestinal blood flow from 53 ± 31 to 83 ± 34 ml/min/100 g.

Discussion

The model that we have developed permits the study of the effects of some of the individual components of the birth process on the cardiovascular adaptations after birth. It should be appreciated that although the ventilatory process we used was very effective because it was possible to maintain oxygenation and also to adequately eliminate carbon dioxide through the lungs when the umbilical circulation was abolished, it does not represent normal respiration. The positive-pressure ventilation used in this preparation could alter some of the responses that might occur with normal respiration, in which inspiration is associated with negative intrapleural pressure. In spite of this, it was possible to obtain valuable information about mechanisms involved in circulatory changes at birth.

The changes in the pulmonary circulation that we observed during each phase of our study are of particular interest. Previous studies done acutely in anesthetized open-chest exteriorized lambs by Dawes et al. (6) indicated that physical expansion of the lung with gas caused some decrease in pulmonary vascular resistance. They estimated that about one-third of the fall in pulmonary vascular resistance could be accounted for by gaseous expansion, the remainder being due to the effects of oxygen. We have confirmed these findings, except that in our studies, the effects of physical expansion of the lung, without altering blood gases, were relatively greater. What was very significant was the finding that in about half the fetal lambs studied, the increase in pulmonary blood flow, and decrease in pulmonary vascular resistance that occurred with rhythmic ventilation alone was almost maximal, and little further change resulted with oxygenation.

The mechanisms by which physical expansion decreases pulmonary vascular resistance have not been delineated. Possibly, the establishment of a gas-liquid interface at the alveolar surface tends to create a negative pressure on the small vessels, thus distending them and reducing vascular resistance. However, more recently, the possibility that lung expansion influences arachidonic acid derivatives, such as prostaglandins and leukotrienes, has been enter-

tained. Thus, Leffler et al. (15) found that expansion of the lung in late gestation fetal lambs caused release of prostacyclin (prostaglandin I_2), which is a potent pulmonary vasodilator. It is not likely, however, that PGI_2 is completely responsible for the decrease in pulmonary vascular resistance associated with ventilation, because indomethacin, a cyclo-oxygenase inhibitor, did not prevent the fall in postnatal pulmonary vascular resistance (16), although it did modify the response. Recently, it has been suggested that leukotrienes may be implicated in perinatal pulmonary circulatory changes. Leukotriene D_4 is a potent pulmonary vasoconstrictor. Administration of either a blocker of leukotriene synthesis, or a putative leukotriene antagonist, results in a marked fall in pulmonary vascular resistance in late-gestation fetal lambs (17). The concept has been considered that the high pulmonary vascular resistance during fetal life is maintained by leukotriene action, and that the decrease after birth is related to removal of this effect. Whether lung expansion could interfere with leukotriene production is yet to be determined.

The decrease in pulmonary vascular resistance and increase in pulmonary blood flow accounts for many of the perinatal circulatory changes. Thus, the increased return of blood through pulmonary veins to the left atrium increases left atrial pressure and decreases the right-to-left flow through the foramen ovale. Also, it accounts for the reduction in right-to-left flow of blood across the ductus arteriosus, and when pulmonary vascular resistance falls markedly, there is a net left-to-right flow through the ductus. Quite apparently from these studies, elimination of the umbilical-placental circulation is not a major hemodynamic event in influencing the circulatory changes.

The increase in peripheral vascular resistance that occurred during lung expansion without oxygenation could be related to reflexes arising from the lungs. Also possibly, associated with the reduced pulmonary vascular resistance, a larger percentage of combined ventricular output is distributed to the lungs. Because combined ventricular output did not increase, the amount distributed to the fetal body falls, and the vascular resistance may increase to maintain arterial pressure.

Blood flow to the brain and the myocardium did not change with ventilation alone, but fell dramatically with oxygenation. This response is related to the profound influence that oxygen delivery has on cerebral and myocardial blood flow (18). The increase in oxygen content associated with ventilation with oxygen causes blood flow to these two organs to fall because oxygen delivery can be maintained with much lower flow rates.

Although many of the circulatory changes occurring after birth can be explained by the events examined in this study, the increase in heart rate and cardiac output was not observed. The lack of these changes could be related to many factors. We have previously shown that fetal lambs subjected to thyroidectomy about two weeks before delivery do not show the expected postnatal increase in heart rate and cardiac output (12). The lambs we studied may not have been subjected to the usual prenatal increase in thyroid hormone activity, and this could account for the lack of response. A second possible explanation is that exposure to cold may be an important factor in initiating a catecholamine response and thus producing the usual cardiovascular response. A third factor that could account for the lack of the response is that the lamb was ventilated by positive pressure. Spontaneous increase in ventilatory activity can increase heart rate in newborn lambs during hypoxemia (19), whereas fetal lambs, which do not show respiratory activity with hypoxemia, develop bradycardia (20).

In conclusion, it is apparent that the experimental model we have developed provides explanations for many of the changes in the circulation that occur during and after birth, but cannot provide mechanisms for all the changes. It will be possible, however, to examine the role of additional perinatal events, such as the effects of administration of hormones to simulate the prenatal surge in plasma hormone concentrations, and of cooling.

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